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Eribulin—A review of preclinical and clinical studies

Umang Swami^{a,1}, Imran Chaudhary^{a,2}, Mohammad H. Ghalib^{a,3}, and Sanjay Goel^{b,*}

^a Albert Einstein College of Medicine, Department of Medical Oncology, Montefiore Medical Center, 1695 Eastchester Road, Bronx, NY 10461, United States

^b Albert Einstein College of Medicine, Department of Medical Oncology, Montefiore Medical Center, 1825 Eastchester Road, Bronx, NY 10461, United States

Abstract

Eribulin mesylate is a non-taxane, structurally simplified, completely synthetic, halichondrin B derivative with an end poisoning, microtubule inhibitory action. Preclinical studies have demonstrated activity in various cancer cell lines and synergistic action with gemcitabine, epirubicin, trastuzumab, cisplatin, docetaxel and vinorelbine. Eribulin has recently been approved by United States Food and Drug Administration as a third line therapy for metastatic breast cancer patients, who have previously been treated with an anthracycline and a taxane. It has also advanced to phase II trials in non-small cell lung cancer, pancreatic, prostate, bladder, head and neck cancers, sarcomas and ovarian and other gynecological tumors. Combination trials with carboplatin, gemcitabine, pemetrexed, cisplatin, and erlotinib are currently ongoing. Eribulin potentially has a low incidence of peripheral neuropathy. The predominant side effects are neutropenia and fatigue, which are manageable. This article reviews the available information on eribulin with respect to its clinical pharmacology, mechanism of action, pharmacokinetics, pharmacodynamics, metabolism, preclinical studies and clinical trials.

Keywords

Breast cancer; EMBRACE; Eribulin; E7389; Halichondrin B; HalavenTM; Microtubule inhibitor; NSC 707389

1. Introduction

In 1985, Hirata and Uemura, originally isolated halichondrin B (NSC 609395), a natural large polyether macrolide from a rare marine Japanese sponge, *Halichondria okadai* and reported its exquisite anticancer activity against murine cancer cells both *in vitro* and *in vivo* [1,2]. Subsequently halichondrin B was isolated from more commonly available sponges belonging to the *Axinella*, *Phakellia* and *Lissodendoryx* families [3–5]. Following the discovery of potent anticancer activity of halichondrin B [2,6] it was tested and compared with other known antimitotic and anticancer agents using the United States (US) National

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* Corresponding author. Tel.: +1 718 904 2488; fax: +1 718 904 2830. sgoel@montefiore.org (S. Goel). ¹ Tel.: +1 718 405 8525; fax: +1 718 405 8527. umangtalking@gmail.com, uswami@montefiore.org (U. Swami). ² Tel.: +1 718 405 8542; fax: +1 718 405 8527. ichaudha@montefiore.org (I. Chaudhary). ³ Tel.: +1 718 405 8515; fax: +1 718 405 8527. mhghalib@montefiore.org (M.H. Ghalib).

Reviewers

Sunil Krishnan, MD, Assistant Professor of Radiation Oncology, MD Anderson Cancer Center, Department of Radiation Oncology, 1515 Holcombe Blvd, Unit 97, Houston, TX 77030, United States.

Monica M. Mita, MD, Institute for Drug Development Cancer Therapy and Research Center, 7979, Wurzbach Road, 4th floor Zeller Bldg #2400, San Antonio, TX 78229, United States.

Cancer Institute's (NCI) 60-cell line screen [7,8]. While antiproliferative patterns of halichondrin B were found similar to those of other antitubulin drugs, its biochemical mechanism of interaction with tubulin was distinct. Although halichondrin B completely inhibited β tubulin β^s intra chain cross link formation (and enhanced β^* formation), noncompetitively inhibited vinblastine binding to tubulin, enhanced bis-5, 5'-[8-(N-phenyl)-amino-naphthalene-1-sulfonic acid] binding to tubulin, and had no effect on iodoacetamide alkylation of tubulin sulfhydryl groups; yet it did not stabilize or inhibit colchicine binding to tubulin. Therefore, it was concluded that the tubulin-based mechanism of halichondrin B is unique from all other known classes of antitubulin agents [8–10]. But even after the confirmation of its potent anticancer activity [11] in the US NCI 60-cell line screen [7] further studies were halted due to lack of availability of sufficient quantities of halichondrin B and its slow and costly procurement. But the drug got a new lease of life in 1998, when Dr. Yoshito Kishi of Harvard developed a completely synthetic halichondrin B and discovered that its cytotoxicity was a function of the macrocyclic lactone C1–C38 moiety [8,12]. Afterwards the synthetic technology was licensed from Harvard to Eisai Research Institute who accomplished the synthesis of the resulting drug, E7389 (NSC 707389) [8,13].

Eribulin mesylate (E7389) is a non-taxane, structurally simplified, completely synthetic macrocyclic ketone analogue of halichondrin B [14]. Although eribulin is characterized in the group of antitubulin drugs that includes vinca alkaloids, dolastatins, cryptophycin, etc., its tubulin interactions appear to be unique. Eribulin inhibits microtubule dynamics via a novel mechanism of action [15–17], which is thought to involve binding to a unique binding site on tubulin [17], resulting in the suppression of microtubule polymerization, without effects on depolymerization, together with sequestration of tubulin into nonfunctional aggregates [15]. By inhibiting mitotic spindle formation, eribulin causes irreversible mitotic block (which ultimately leads to cell cycle arrest in the G2-M phase) and apoptosis [15–18]. Based on the novel mechanism of action of eribulin, which is distinct from other known classes of tubulin-targeted agents, and its encouraging preclinical activity, it was hypothesized that eribulin may have efficacy in patients with malignancies that are resistant to other tubulin-targeted agents together with a more favorable tolerability profile. Eribulin was presented to NCI, Drug Development Group in 1998 and entered phase I clinical trials in 2002. On November 15, 2010, U. S. Food and Drug Administration approved eribulin for treatment of patients with metastatic breast cancer (MBC) who have previously received an anthracycline and a taxane in either the adjuvant or metastatic setting, and at least two chemotherapeutic regimens for the treatment of metastatic disease [19]. Currently eribulin is in phase II trials for non-small cell lung cancer, pancreatic, prostate, head and neck cancer, bladder and ovarian and related gynecological tumors and in phase III clinical trial as second line therapy for the treatment of advanced and MBC. The trials are taking place across the world under the sponsorship of Eisai and NCI [20].

The purpose of this article is to review the available information on eribulin with respect to preclinical studies, clinical pharmacology, mechanism of action, pharmacokinetic and pharmacodynamic properties, results of various phase I, II, III trials, clinical efficacy for breast cancer, adverse-effect profile and dosage and administration. Data from studies using eribulin in combination with other chemotherapeutic agents are also reported.

2. Materials and methods

Relevant English-language literature was identified through searches of PubMed (1966 to July 2010), International Pharmaceutical Abstracts (1977 to July 2010), and proceedings of international conferences on Oncology (January 1995 to July 2010). Search terms included Eribulin, E7389 and Halichondrin B. The references of the identified articles were reviewed for additional sources. Additional product information was obtained from Eisai Medical

Research Inc. Studies from the identified literature that addressed this article's objectives were selected for review, with preference given to Phase I and II trials.

3. Pharmacology

Eribulin mesylate (also known as eribulin mesilate, INN codename E7389, and before that, ER-086526 and B-1939, US NCI designation NSC-707389) [19,21,22] is a white crystalline hygroscopic powder with a molecular weight of 826.0 g/mol and molecular formula of $C_{40}H_{59}NO_{11} \cdot CH_4O_3S$ [19,23]. The structures of halichondrin B and eribulin are given in Figs. 1 and 2.

Chemical structure names [19,21,23]:

- (2R,3R,3aS,7R,8aS,9S,10aR,11S,12R,13aR,13bS,15S,18S,21S,24S,26R,28R,29aS)-2-[(2S)-3-amino-2-hydroxypropyl]-3-methoxy-26-methyl-20,27-dimethylidenehexacosahydro-11,15:18,21:24,28-triepoxy-7,9-ethano-12,15-methano-9H,15H-furo[3,2-i]furo[2',3':5,6]pyrano[4,3-b][1,4]dioxacyclopentacosin-5(4H)-one methanesulfonate (salt).
- 11,15:18,21:24,28-Trieпоxy-7,9-ethano-12,15-methano-9H,15H-furo[3,2-i]furo[2',3':5,6]pyrano[4,3-b][1,4]dioxacyclopentacosin-5(4H)-one, 2-[(2S)-3-amino-2-hydroxypropyl]hexacosahydro-3-methoxy-26-methyl-20,27-bis(methylene)-, 2R,3R,3aS,7R,8aS,9S,10aR,11S,12R,13aR,13bS,15S,18S,21S,24S,26R,28R,29aS)-, methanesulfonate (salt).

The eribulin structure is of a simplified macrocyclic ketone in which the C1 lactone ester of halichondrin B is replaced by ketone, the entire C39–C54 polyether side-chain is removed, C31 methyl is replaced by methoxy and the tri-cyclic C29–38 system is replaced by a single five membered ring.

Eribulin is freely soluble in water, methanol, ethanol, 1-octanol, benzyl alcohol, dimethylsulfoxide, N-methylpyrrolidone, dichloromethane and ethylacetate, soluble in acetone, sparingly soluble in acetonitrile, practically insoluble in tert-butylmethyl ether, n-heptane and n-pentane. In Britton–Robinson buffer, E7389 is freely soluble at pH 3–7, soluble at pH 9 and slightly soluble at pH 11. Eribulin is stored at 25 °C/77 °F (not to be frozen). Eribulin, which is prepared in an aqueous solution, has a short infusion time, can be administered with or without dilution, does not require steroid or antihistamine premedications and protection from light, is not necessary. These are the distinct advantages of eribulin as compared to currently approved microtubule-targeting agents [19,23].

4. Preclinical studies

4.1. In vitro studies

In the *in vitro* studies, cell growth was inhibited at sub to low nmol/L IC_{50} values (0.09–9.5 nmol/L) by eribulin in a wide variety of established human cancer cell lines, including MDA-MB-231, -435, -468 and HCC1806 breast cancers, HT-29, COLO 205 and DLD-1 colon cancers, H23, H441, H520 and H522-T1 non-small cell lung carcinomas (NSCLC), NCI-H82 small cell cancer, DU 145 and LNCaP prostate cancers, U937 histiocytic lymphoma, FaDu pharyngeal squamous cell carcinoma (head and neck cancer), A2780/1A9 ovarian cancer, MES-SA uterine sarcoma, HL-60 promyelocytic leukemia, and LOX melanoma [8,23,24].

Eribulin was found to inhibit MDA-MB-435 cell growth at sub-nM levels (IC_{50} = 0.09 nM) with greater potency than vinblastine (IC_{50} = 0.59 nM) or paclitaxel (IC_{50} = 2.5 nM) [8]. Similar low, nanomolar or subnanomolar activity was seen for eribulin against colon cancer

COLO 205 and DLD-1, prostate cancer DU 145 and LNCaP, melanoma LOX, leukemia HL-60 and lymphoma U-937 cells, with mean IC₅₀ value 1.8 nM (ranging from 0.09 to 9.5 nM) and was found to be roughly 2–4 fold more potent than vinblastine and paclitaxel (two tubulin based antimitotic agents run as internal standards in each experiment) and similar to its natural precursor halichondrin B. Though growth of several human cancer cell lines were inhibited at subnM concentrations, eribulin did not show cytotoxic effects with concentrations up to 1 μ M against dormant IMR-90 human fibroblasts, indicating that growth inhibition by lower sub-nM levels of eribulin is specific for proliferating cells and not secondary to nonspecific cytotoxicity [8]. Experiments on the NSCLC cell lines A549 (wild type p53) and Calu-1 (p53-null) showed p53-independent anticancer activity of eribulin in the 0.5 pM range which was clinically achievable [25]. Though eribulin showed virtually similar activity as natural halichondrin B in NCI 60 cell line screen [8,24], it was found to be more potent in its interactions with tubulin [17] and *in vivo* studies as well as less toxic as seen in granulocyte-macrophage colony forming units [26].

Further *in vitro* studies were done in SK-BR-3 cell line to study synergistic combinations of eribulin with conventional drugs used for breast cancer treatment. Eribulin demonstrated synergistic activity when combined with gemcitabine, cisplatin, epirubicin, trastuzumab, docetaxel and vinorelbine. When combined with carboplatin it showed additive effects and antagonistic effects when combined with 5'-DUFR [27]. Eribulin in combination with carboplatin demonstrated antagonism in some NSCLC cell lines while additive response in others [24]. Experiments with paclitaxel resistant ovarian cancer sublines A2780/1A9, 1A9PTX10 and 1A9PTX22 revealed that eribulin retained full *in vitro* potency in cells harboring beta-tubulin mutations that leads to substantial resistance to taxanes [28].

4.2. In vivo studies

Human tumor xenograft studies in mice (breast, lung, ovary, colon, melanoma, pancreatic, and fibrosarcoma) demonstrated tumor regressions, remissions and an increased lifespan at dose levels below the maximum tolerated dose (MTD) [8,23]. Eribulin showed significant and superior *in vivo* anticancer efficacy in MDA-MB-435, COLO 205 and LOX cell lines (in NIH:OVCAR-3 model, significant only) at much lower doses (0.05–1 mg/kg i.v. or i.p.) as compared to paclitaxel, run at empirically determined MTD levels. In the MDA-MB-435 model, treatment with 0.25–1.0 mg/kg eribulin resulted in actual regression of measurable tumors by day 14, >95% inhibition at day 42 with no evidence of cytotoxicity. All doses of eribulin were found to be either equally efficacious (0.25, 0.5 mg/kg) or superior (1 mg/kg) to paclitaxel (MTD = 25 mg/kg) in the breast model. In LOX melanoma model eribulin (0.05 mg/kg) inhibited tumor growth by 78% on day 17 and higher doses resulted in complete tumor suppression. Eribulin (0.5 mg/kg) treated mice showed a significantly delayed tumor regrowth rate as compared to paclitaxel (12.5 mg/kg), with 30% becoming tumor free by day 17 and remaining so for 7 months. Eribulin was found to be more potent in NIH: OVCAR-3, COLO 205, LOX and MDA-MB-435 models by 20, 40, 50 and 100 folds respectively as compared to paclitaxel running at MTD levels [8].

Moreover, eribulin showed significantly wider *in vivo* therapeutic windows (5-fold in LOX and 4-fold in MDA-MB-435 models), in comparison to paclitaxel (<2.0 in the LOX model and 1.7 in the MDA-MB-435 model). This wide therapeutic window is particularly important, as it leads to the possibility to augment doses, 4–5 times above fully tumor-suppressive dose, leading to more complete eradication of residual tumor cells and contributing to substantial *in vivo* efficacy. This might also explain its superiority over paclitaxel due to latter's small therapeutic window. The reasons for this unusually wide therapeutic window of eribulin are not currently known [8,24].

Towle et al. with dose scheduling studies on MDA-MB-435 showed that maximal efficacy and minimal toxicity is achieved with moderate intermittent dosing such as Q2D $\times$ 3 [$\times$ 3 weeks], Q4D $\times$ 3 and Q7D $\times$ 3 [29]. Further studies with Q4D $\times$ 3 schedule in HT-1080 (fibrosarcoma) mice xenograft model showed long-lasting tumor regression at all doses (1.3–4.0 mg/kg). Eribulin resulted in 10 of 10 (100%) and 9 of 10 (90%) mice being rendered tumor free by day 38 and day 42 at dose 1.7 mg/kg (maximal tolerated dose) and 1.3 mg/kg respectively. In PANC-1 (pancreatic cancer) also doses from 0.4 to 4 mg/kg produced long lasting remissions with Q4D $\times$ 3 schedule [29]. In MDA-MB-435 (breast cancer) model Q4D $\times$ 3 treatment at 0.375–1.5 mg/kg/dose led to complete tumor regression in 14 of 15 animals with 24–41 day remission. In NCI-H522 (lung cancer) xenograft model Q4D $\times$ 3 treatment at 0.375–1.5 mg/kg/dose led to complete tumor regression in 14 of 15 animals with at least 37-day remission [26].

In vivo synergistic ability of eribulin was tested with gemcitabine, doxorubicin, docetaxel, and carboplatin [24,29]. Eribulin 0.1–0.4 mg/kg and q4d $\times$ 3 schedule (limited tumor inhibitory effect) when combined with gemcitabine 120–270 mg/kg and q3d $\times$ 4 schedule (only tumor stasis effect) induced significant regression in H522 NSCLC xenografts [29]. However eribulin combination with doxorubicin was not synergistic in the MDA-MB-435 xenograft model [24,29].

Eribulin showed no statistically significant adverse effect on caudal nerve conduction velocity (NCV), digital NCV and amplitude in caudal and digital nerves in mice at MTD. Whereas in comparison both paclitaxel and ixabepilone treated mice at MTD demonstrated statistically significant reduction in caudal and digital NCV and amplitude. Also the pathological changes in mice at equivalent half MTD or higher doses in dorsal and sciatic root ganglia were milder and less frequent with eribulin as compared to ixabepilone and paclitaxel[30].

4.3. Pharmacodynamics and mechanism of action

Halichondrin B binds tubulin at a site close to the vinca site altering depolymerization [7], with no effect on colchicine binding [9]. It inhibits the formation of an intra-chain cross-link between two sulfhydryl groups in β -tubulin, does not affects alkylation of tubulin sulfhydryl groups by iodoacetamide (unlike vinblastine) and enhances the exposure of hydrophobic areas on the tubulin molecule. The unique mechanism of cytotoxicity of the halichondrins is secondary to a specific conformational effect as a function of the macrocyclic lactone C1–C38 moiety [8–10] that suppresses microtubule growth without effect on microtubule shortening (unlike conventional anti-tubulin agents like taxanes, epothilones, and vinca alkaloids which inhibit both growth and shortening of micro-tubules) and sequester tubulin into nonfunctional aggregates [15].

Eribulin is a strong competitive inhibitor of halichondrin B binding to tubulin [31]. It inhibits cancer cell growth via induction of irreversible complete mitotic block at G₂-M (prometaphase blockage), disruption of mitotic spindles formation and initiation of apoptosis following prolonged mitotic blockage [8,18]. The antimitotic mechanism of eribulin is different from other microtubule-targeted agents such as vinblastine, vincristine and paclitaxel as revealed by experiments on human breast cancer MCF7 and human osteosarcoma U-2 OS cells [15,32,33]. Eribulin exerts its antiproliferative action via a novel tubulin targeted mechanism. It predominantly inhibits microtubule dynamics and tubulin polymerization into microtubules rather than shortening (unlike other antitubulin agents) (Fig. 3) [8,15,32,33]. It acts via an end poisoning mechanism, resulting in micro-tubule growth inhibition and tubulin sequestration into non-functional aggregates [15]. Eribulin at lowest effective concentration may suppress mitosis by either directly binding as unliganded eribulin to microtubule ends or by competing with unliganded soluble tubulin for addition to

growing microtubule ends by inducing tubulin aggregates. This leads to formation of dysfunctional mitotic spindles that cannot pass the metaphase/anaphase checkpoint [15].

At 100 nM (concentration that inhibits microtubule plus end growth by 50% or concentration approximately 10-fold higher that minimally induces complete G2/M blocks based on dose/response studies) eribulin suppresses dynamic instability at microtubule plus ends by binding with high affinity but does not suppress dynamic instability at microtubule minus ends [23,34]. Eribulin potently inhibits microtubule dynamics, with only a single bound eribulin molecule per two microtubules inducing a 50% reduction in growth rate [35]. Eribulin inhibits tubulin polymer formation by possibly binding to either the interdimer interface or the β -tubulin subunit alone. It does not bind to both α - and β -tubulin [34,36]. A significant correlation has been demonstrated between β III tubulin expression levels in cancer cell lines and sensitivity to eribulin, suggesting tumors expressing higher levels of β III tubulin isotype may be more responsive to eribulin [37]. This may help as β III tubulin gene is found to confer resistance to [38] and is inducible by [39] various antitubulin agents like vinorelbine and paclitaxel. Also its overexpression has been found to be correlated either with low response rates in patients treated with regimens containing taxanes or vinorelbine or with reduced survival in patients with non-small cell lung cancer, in breast, ovarian, and gastric cancers, and in cancers of unknown primary site [40].

5. Pharmacokinetics and metabolism

5.1. Pharmacokinetics

The first phase I study was conducted by California Cancer Consortium, with eribulin administered as a 1–2 min weekly bolus every 3 weeks out of 4. It demonstrated a tri-phasic elimination with prolonged terminal half-life of 36–48 h. At the MTD, plasma levels of eribulin were above concentrations required for *in vitro* cytotoxicity for >1 week [41]. After 48 h a mean of $10 \pm 1\%$ of the dose was recovered in the urine [42].

Another study at our site was conducted with a 1-h i.v. infusion on days 1, 8 and 15 of 28 day cycle. Eribulin pharmacokinetics was linear and dose-proportional over the dosing range of 0.25–1.4 mg/m² (Fig. 4). Eribulin exhibited consistent pharmacokinetic parameter estimates between the first and third i.v. doses administered on days 1 and 15 at each dose level. The plasma concentration–time profile exhibited a rapid distribution phase with a mean distribution half-life of ≈ 0.43 h followed by a slower elimination phase with a half-life of 38.7 h. Again a minimal urinary excretion was seen with 5–6% of the administered dose eliminated in urine over a 72-h period after a single dose [10].

Eribulin administered as a 1 h eribulin infusion every 21 days also showed linear kinetics, terminal half-life of 2 days, rapid extensive volume of distribution, slow-to-moderate clearance and slow elimination, with non renal clearance ($\approx 7\%$ of the drug excreted unchanged in the urine) [43].

In a separate study, no difference was observed between day 1 and day 8 pharmacokinetic profiles with 5 min eribulin i.v. bolus given on day 1 and 8 every 21 days. The systemic clearance on day 1 was 1.50–2.69 L/h/m² and the volume of distribution was 93.4–106.8 L/m² [44].

In a phase I study done on patients with liver impairment, eribulin was generally safe and well tolerated. Hepatic impairment decreased clearance and prolonged elimination half-life. The mean dose-normalized $C_{\max}$ ratio estimate of eribulin between patients with normal and mildly impaired hepatic function was 1.1 but between normal and moderate hepatic impairment was 1.5. The mean dose-normalized $AUC_{(0-\infty)}$ increased 1.7-fold (mild) and

2.8-fold (moderate) as compared to patients with normal hepatic function. In summary, eribulin exposure increased with worsening hepatic function. A comparative data is presented in Table 1 [45].

In an open label, pharmacokinetic, two sequence, two-way crossover trial, effect of co-administration of ketoconazole, a strong CYP3A4 and P-glycoprotein (PgP) inhibitor was evaluated on 12 patients with advanced solid tumors. There were no treatment related serious adverse events during the study phase of the study (cycle 1 only). The mean dose normalized AUC values were similar when eribulin was administered with or without ketoconazole indicating eribulin can be safely co-administered with CYP3A4 inhibitors [46]. Population pharmacokinetic analyses also showed that CYP3A4 inhibitors and inducers have no effect on eribulin exposure [46]. The pharmacokinetic analyses of combination trial of eribulin with carboplatin suggested absence of any interaction [47]. A recently conducted phase II study evaluated eribulin (1.4 mg/m² i.v. bolus on days 1 and 8 of 21 day cycle) pharmacokinetics in heavily pretreated, locally advanced or MBC patients. A three-compartment model best described eribulin pharmacokinetics, with elimination from the central compartment. As seen in above other studies distribution was rapid with slow elimination. In patients with adequate organ functions [AST < ULN and creatinine clearance = 101 mL/min (Cockcroft-Gault)], clearance was 2.98 L/h and central volume of distribution was 3.72 L (V₁). Volumes for the two peripheral compartments were 3.60 L and 126 L and inter-compartmental clearances were 2.7 L/h and 5.6 L/h respectively. An inter-patient clearance variability of 57% (range 26–98% for other parameters) was obtained with a 21% residual error (proportional). In patients with elevated AST, clearance on an average was 38% lower and positively correlated with the renal function. Appreciable interpatient pharmacokinetic variability was observed, a minor fraction of which was explained by measures of liver and renal function [48] (Table 2).

5.2. Metabolism

Eribulin is a substrate for PgP drug efflux pump and shows reduced *in vitro* activity against multidrug resistant cells which overexpress PgP drug efflux pump [49]. The IC₅₀ of eribulin on PgP mediated digoxin transport activity was estimated to be greater than 10 µmol/L, indicating that eribulin is a weak PgP inhibitor. The transport of digoxin is reduced in the presence of 1 µmol/L eribulin [23]. As discussed earlier although eribulin is a PgP drug efflux pump substrate it retains full *in vitro* activity against taxane-resistant PTX10 and PTX22 human ovarian cancer cells, which are resistant due to β-tubulin mutations, suggesting that eribulin may show clinical effectiveness in taxanes refractory tumors harboring β-tubulin mutations [28,50]. Unchanged drug was found to be the major component in plasma, bile, urine and feces following i.v. dosing in intact and bile duct cannulated rats and dogs. Eribulin is not strongly bound to mouse, rat, dog or human plasma protein with a species difference suggesting that any variability in either albumin or α₁-acid glycoprotein will not significantly affect eribulin pharmacokinetics [23,24]. Eribulin is primarily eliminated unchanged in the feces [19].

CYP3A4 appears to be the major enzyme responsible for the human hepatic metabolism of eribulin *in vitro*. The metabolites formed by CYP3A4 mediated reactions were predominantly the four isomeric monohydroxylates [23]. There is no major metabolite of eribulin in humans [19]. Eribulin does not induce CYP1A and CYP3A expression or activities. [51]. No significant inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP2E1 was detected with E7389 at concentrations up to 5 µM [23]. Although eribulin competitively and reversibly inhibits the testosterone 6-beta-hydroxylation, nifedipine dehydration and R-warfarin 10-hydroxylation activities of recombinant CYP3A4 (apparent Ki 3–17 µM), it does not induce or inhibit hepatic CYP3A4 activity nor does it inhibits

CYP3A4-mediated metabolism of various therapeutic agents, including carbamazepine, diazepam, paclitaxel, midazolam, tamoxifen, or terfenadine at clinically relevant concentrations [24,51]. Therefore, it would not be expected to inhibit the metabolism of concurrently administered drugs that are metabolized by CYP3A4 or CYP1A, suggesting a minimal risk of drug–drug interactions [23,51]. Eribulin, in a manner similar to terfenadine acts as a CYP3A4 substrate competitor and not as a mechanism-based inhibitor [51].

6. Clinical trials: safety and efficacy

6.1. Phase I studies

The first phase I trial was conducted at the California Cancer Consortium on patients with refractory or advanced solid tumors [41]. It followed a rapid titration design with real-time pharmacokinetic analysis to guide dose escalation [52]. Starting dose was 0.125 mg/m²/week. A total of 40 (38 evaluable) entered the study. The rapid escalation phase, which enrolled single patient cohorts with intra- and inter-patient dose doubling till toxicity was observed, ended with a grade 3 alkaline phosphatase at 0.5 mg/m²/week. The second phase consisted of a standard 3 + 3 dose escalation schedule, which ended at 2.0 mg/m²/week with two dose limiting toxicities (DLT's); 1 grade 3 febrile neutropenia and 1 grade 4 neutropenia. Other serious non-hematological toxicities included hypoglycemia, hypophosphatemia, and fatigue. The MTD was 1.4 mg/m²/week. Two partial responses (PR, NSCLC; bladder), three marginal responses (NSCLC, breast, and thyroid) and twelve patients with stable disease (SD, median of 4 months; range 2–14 months) were observed [41].

In a second phase I trial conducted jointly by CTCRC and our institution [10], patients received a 1-h i.v. infusion of eribulin on days 1, 8 and 15 of a 28-day cycle. Thirty-two patients were treated following the NCI accelerated titration scheme design 4B [52]. The median numbers of cycles received were 2 (range, 1–10). At 1.4 mg/m² (highest dose level), DLT of grade 4 neutropenia was seen in two patients and one of these patients also experienced grade 3 fatigue. Three other patients at the 1.4 mg/m² dose level experienced grade 3 neutropenia (not DLT) leading to the omission of the planned week 3 dose in cycle 1. These events showed that eribulin at 1.4 mg/m² cannot be administered on the planned schedule; therefore, the MTD in this study was regarded as 1.0 mg/m². The most common eribulin-related adverse events included fatigue [53% of patients (40% grade 1/2, 13% grade 3, no grade 4)], nausea [41% of patients (all grade 1/2)], and anorexia [38% of patients (35% grade 1/2, 3% grade 3, no grade 4)]. Eribulin related grade 3 and 4 toxicities included neutropenia (19%), fatigue (13%), anorexia (3%), anemia (3%) and vomiting (3%). Eribulin was found to be fairly safe, associated with a low incidence of neuropathy (25%, all grade 1/2) or cumulative toxicities in the twelve patients treated for three or more cycles and an absence of hypersensitivity reactions. Responses included an unconfirmed PR (lasting 79 days) in a patient with cervical cancer and SD (ranging from 39 to 234 days) in ten patients [10].

Another phase I trial involved 21 patients with advanced solid tumors and used a 1 h infusion on day 1 of 21-day cycle [43]. Doses ranged from 0.25 to 4 mg/m² and dose escalation involved two-stage design based on design 3B of Simon et al. [52]. Febrile neutropenia as DLT was seen in all three patients at 4 mg/m², two of the three patients at 2.8 mg/m² (on one dose reduction) and one of seven patients at 2.0 mg/m² dose levels. Thus MTD with this schedule was established at 2.0 mg/m². The most frequently reported drug related adverse events (all grades) were neutropenia, fatigue (all grade 1 or 2), alopecia (all grade 1 or 2), febrile neutropenia, anemia (all grade 1) and nausea (all grade 1) in 38%, 33%, 33%, 29% and 24% patients respectively. Seven patients experienced treatment related serious adverse events which were: grade 3 hyponatremia (1 patient), grade 4 febrile

neutropenia (five patients) and grade 4 febrile neutropenia, grade 2 pyrexia, and grade 3 infection (one patient). Eribulin associated neutropenia exhibited a nadir 7–15 days after the first treatment with recovery to normal by the end of the 21-day cycle. Another important hematological toxicity was grade 1 thrombocytopenia (10%). Only one grade 1 peripheral neuropathy occurred at 4-mg/m². Responses included an unconfirmed PR in NSCLC patient at 4 mg/m² (received 4 cycles) and SD in twelve patients with median duration of 86 days (range 47–386 days) [43].

A fourth phase I study involved the use of a 5-min eribulin i.v. bolus on day 1 and 8 of 21 days cycle in 15 patients. Three, three, six and three patients were treated at 0.7, 1.0, 1.4 and 2.0 mg/m² drug cohorts respectively. Cycles ranged from 1 to 15 with 7 patients receiving more than 4 cycles. Observed DLTs were grade 4 neutropenia and febrile neutropenia. The most commonly observed toxicity was neutropenia and was easily managed. Other frequently observed non-hematological toxicities (generally mild) were fatigue, alopecia, nausea, anorexia, neuropathy, liver enzyme elevations, hyperglycemia, and increased CRP levels. Grade 3 toxicities were fatigue (2 patients) and elevation of GGT (Gamma-glutamyltransferase, 1 patient). PR in three patients (two with NSCLC and one with head and neck cancer) at 1.4 mg/m² and SD (more than 12 weeks) in three patients were achieved during the trial. A dose of 1.4 mg/m² administered on days 1 and 8 every 3 weeks was recommended for phase II studies [44].

In a phase I trial on patients with liver dysfunction the most common treatment-emergent adverse events were alopecia, nausea and fatigue in 7, 5 and 4 patients respectively. Adverse events probably related to treatment included neutropenia and peripheral neuropathy in 3 and 1 patient respectively. Most of the former (3 of 4) resolved without dose reduction. Patients with mild hepatic impairment experienced highest incidence of adverse events. There were no deaths, treatment-related serious adverse events or discontinuations during the study phase of the study (cycle 1 only) [45].

In a first-in-human phase I study of eribulin in patients with renal dysfunction and advanced urothelial cancer (UC), eribulin was given in tiers of 0.7, 1.0 and 1.4 mg/m² IV on days 1 and 8, every 3-week. The median number of cycles was 6 [53]. MTD in moderate renal dysfunction (40–59 mL/min, Cockcroft-Gault) arm was 1.4 mg/m² with no DLTs. In severe renal dysfunction (20–40 mL/min, not needing dialysis) arm 1 out of 6 patients treated at 1.4 mg/m² had DLT (grade 3 weakness and fatigue). Of the 20 evaluable patients, 3 achieved PR and 9 had SD. Of these 9 patients, 2 patients had unconfirmed PR on 6 week scans but progressive disease at 12 weeks. Median progression-free survival (PFS) was 4.1 months and median survival was 9.7 months at a median follow-up of 11 months. Toxicities seen were grade 3/4 neutropenia, febrile neutropenia, grade 1 sensory neuropathy and grade 1 transaminitis in 5, 1, 7 and 8 patients respectively. Tolerance of full doses of eribulin and encouraging activity may fulfill an unmet need across a spectrum of cancers in patients with renal dysfunction [53].

A phase I combination study of eribulin and gemcitabine was initiated in patients with advanced solid tumors based on synergistic action in H522 NSCLC xenografts. Twenty-one patients were treated and one PR was obtained in ovarian cancer. Eight patients had SD with four showing minor response (2 NSCLC, 1 endometrial and 1 head and neck cancer). DLTs were grade 3 diarrhea and grade 3 dizziness/fatigue (1 patient each). Other drug related grade 3 and 4 treatment related toxicities were neutropenia (6 patients), leukopenia (3 patients), anemia (2 patients) and thrombocytopenia (2 patients). Dose determined for phase II investigation is eribulin 1.0 g/m² and gemcitabine 1000 mg/m² every 3 weeks [54].

Another phase I combination trial of eribulin in combination with carboplatin is currently ongoing. Carboplatin is given as 30-min IV infusion and eribulin by 2- to 5-min IV bolus, separated by 1 h. In stage 1, eribulin mesylate (0.7, 0.9, 1.1, and 1.4 mg/m²) was dose escalated with carboplatin at a fixed AUC of 5 in a 3 + 3 design in two sequences, differing by the order of administration. In stage 2, eribulin (1.1 and 1.4 mg/m²) was dose escalated with carboplatin at a fixed AUC of 6 using the preferred schedule from stage 1. Fifty two patients have been treated. In stage 1, a DLT (diarrhea) was experienced in 1 out of 5 patients at 1.4 mg/m² in the carboplatin-first schedule and in 0/3 patients in the eribulin-first schedule, defining the MTD as 1.4 mg/m² (same as the monotherapy dose) with eribulin given first. In stage 2, eribulin was given first and DLTs occurred in 1/6 patients (febrile neutropenia) at 1.1 mg/m² and in 2/3 patients (febrile neutropenia, neutropenia) at 1.4 mg/m², defining the MTD as 1.1 mg/m². Most frequent adverse events were neutropenia (52%; 40% grade 3/4), thrombocytopenia (29%; 13% grade 3/4), fatigue (58%; 4% grade 3/4), and nausea (40%; no grade 3/4). One complete response (CR) in tonsillar cancer and two PRs in prostate cancer were observed by RECIST. An extension arm with the combination at recommended phase II doses (eribulin mesylate 1.1 mg/m², carboplatin AUC6) is enrolling patients with chemo-naïve, advanced non-small cell lung cancer [47].

6.2. Phase II trials

6.2.1. Breast cancer—Further development of eribulin in phase II and III trials continued with the bolus 1.4 mg/m²/week, eribulin on days 1, 8, and 15 of a 28-day cycle schedule as recommended by the California Cancer Consortium study [41]. However due to neutropenia in many patients on day 15 leading to dose interruption or omission, treatment schedule was modified to days 1 and 8 of a 21-day cycle which appeared to be more favorable [55,56] (Fig. 5).

The first large phase II trial of eribulin in breast cancer was an open-label, single-arm, Simon's two-stage, multicenter study with 23 sites in USA and enrolled MBC patients, who had received prior therapy with at least an anthracycline and a taxane. The primary objective was to assess the overall response rate (ORR) to eribulin in heavily pretreated patients with MBC. Secondary objectives were to evaluate duration of response (DOR), PFS, overall survival (OS), and safety. Patients received eribulin mesylate (1.4 mg/m²) as a 2- to 5-min intravenous (IV) infusion on days 1, 8, and 15 of a 28-day cycle. But as discussed above, due to recurrent neutropenia on day 15 requiring dose delays beyond 28 days, treatment schedule was modified with eribulin on days 1 and 8 of a 21-day cycle. A total of 103 patients with median number of 4 prior chemotherapies (range 1–11 regimens) were treated. In the protocol-defined population ($n = 87$), eribulin achieved an independently reviewed ORR (all PRs) of 11.5% and a CBR of 17.2%. The median DOR was 171 days (5.6 months; range, 44–363 days), the median PFS was 79 days (2.6 months; range 1–453 days), and the median OS was 275 days (9.0 months; range 15–826 days). The six-month PFS and OS were 25.9% and 67.8% respectively. The most common drug-related grades 3–4 toxicities were neutropenia, leukopenia, fatigue, peripheral neuropathy and febrile neutropenia in 64%, 18%, 5% and 4% patients respectively. The 21 day schedule appeared to be associated with a more favorable tolerability profile than the 28-day schedule [56] (Table 3).

A second, Eisai sponsored phase II trial in breast cancer was also a non-randomized, open label, single arm, multi-center ($n = 78$) trial that assessed the efficacy and safety of eribulin (1.4 mg/m² administered as a 2–5 min i.v. bolus on days 1 and 8 of a 21-day cycle) in locally advanced or MBC patients previously treated with an anthracycline, a taxane and capecitabine. The primary objective was assessment of ORR (assessed by independent review using RECIST criteria). The secondary objectives were assessment of DOR, PFS, OS and adverse events. Of the 299 patients enrolled, 291 received eribulin (safety population)

but efficacy analysis was done on 269 patients who met key inclusion criteria (eligible population). The eligible population had a median age of 56 years with a median of 4 prior chemotherapy regimens. In total 71% of them were ER+ or PgR+, 11% HER2/neu+ and 20% were triple (ER, PgR and HER2) negative. Median number of eribulin cycles was 4 (range 1–27). ORR as determined by investigator was 14.1% (1 CR, rest all PRs) with a CBR of 19.7%. Independent review determined ORR was 9.3% (all PRs) and CBR was 17.1%. SD was seen in 46.5% with a median DOR of 3.5 months (106 days; range 42–258 days), median PFS of 2.6 months (78; 1–398 days) and median OS of 10.4 months (315; 19–604 days). The six-month PFS and OS rates were 12.4% and 72.3%, respectively. Highest CBR was observed in ER+ and/or PgR+ subgroup (21.4%) and least CBR was observed in triple ER/PgR/HER2 negative subgroup (3.7%). The most frequently reported treatment-related grade 3/4 toxicities were neutropenia (54%; febrile neutropenia: 5.5%), leukopenia (14.1%), and asthenia/fatigue (10%; no grade 4). Grade 3 peripheral neuropathy occurred in 6.9% of patients with no grade 4. No death was “probably” related to eribulin and only one death with unknown cause was considered “possibly” related to study treatment [55].

Overall across these two studies, the rate of neuropathy was around 32%, with 26% grade 1/2, 5–7% grade 3 and no grade 4 incidences. Thus eribulin was associated with a manageable level of neuropathy, and pre-existing neuropathy usually did not worsen with eribulin treatment [55,56]. However, it should be noted that both trials excluded patients with neuropathy above grade 2. It therefore calls for prudence and care in patients with prior taxane exposure and residual neuropathy.

Another single-arm, open-label phase II study evaluated the efficacy and safety of eribulin in Japanese patients with locally advanced or MBC previously treated with an anthracycline and a taxane. Patients with 3 prior chemotherapies in metastatic setting were enrolled. The primary efficacy endpoint was ORR as assessed by independent review using RECIST criteria. Eighty one patients with median age of 54 years received a median of 5 cycles (range 1–20; 1.4 mg/m² eribulin i.v. bolus on days 1 and 8 of a 21-day cycle). In total 65% of them were ER- or PgR-positive, 11.3% HER2/neu-positive and 27.5% were triple negative. The median number of prior chemotherapy regimens was 3. An ORR of 21.3% with all PRs (17 patients) was observed, along with 37.5% SD and CBR of 27.5%. The median DOR was 119.0 days, median PFS was 112.0 days and median OS was 331.0 days. Six-month PFS and OS rates were 20.1% and 72.3%, respectively. The most frequent treatment-related grade 3/4 toxicities were neutropenia, leukopenia, febrile neutropenia and lymphopenia in 95.1%, 74.1%, 13.6% and 12.3% respectively. An incidence of 3.7% grade 3 peripheral neuropathy was observed with no grade 4 [57]. The role of eribulin in breast cancer has been reviewed previously [14,58].

6.2.2. Non-Small cell lung cancer—Based on activity in xenograft models, an open-label, single-arm, phase II study of eribulin was conducted in patients with advanced NSCLC [59]. Patients with ECOG performance status of 0 or 1 and prior progression with platinum-based doublet chemotherapy were recruited. Eribulin was administered with a 28 day schedule (1.4 mg/m² eribulin bolus infusion on days 1, 8, and 15 of a 28-day cycle) which was later changed to 21 day schedule (eribulin on days 1 and 8 of a 21-day cycle) due to dose delays and omissions on day 15 secondary to myelosuppression like in phase II breast trials [56]. Patients were enrolled in two strata based on prior taxane exposure. A total of 103 patients (83 with prior taxane therapy and 20 taxane naïve) with 77 on 28 day schedule and 26 on 21 day schedule were treated. Among the enrolled patients, the median age was 65 years and median number of prior therapies was 2. The primary efficacy endpoint was ORR confirmed by independent radiologic review. A median number of 3 cycles (range 1–15) were administered. Observed drug related toxicities were neutropenia [grade 3 (23%) and 4 (26%)], febrile neutropenia (4%), grade 3 fatigue (11%), grade 3

nausea (2%), and peripheral neuropathy [grade 1/2 (37%) and 3 (2%)]. Grade 3–4 nausea, fatigue, pyrexia and dehydration were more frequently observed in the 28-day cohort compared to 21-day cohort. Based on RECIST criteria, the ORR (all PRs) was 9.7%, with 10.8% PR in taxane pre-treated, and 5% PR in taxane naïve patients. Overall disease control rate (PR + SD) was 55.3%, 12-week PFS was 53.0% and median PFS was 102 days (range 1–408+ days). Median DOR was 176 days (range 50–291+ days), and median OS was 287 days (range 16–423+ days). The one-year survival rate was 46.4% [59]. Seeing the encouraging activity of eribulin, other trials using eribulin in combination with pemetrexed, erlotinib and carboplatin (extension arm of phase I study) are currently ongoing in NSCLC patients [20,47,59].

Another phase II trial of eribulin in prior taxane-treated NSCLC patients was conducted under the sponsorship of California Cancer Consortium [60]. Eligibility criteria included histologically or cytologically confirmed advanced NSCLC with measurable disease, previous treatment with platinum-based therapy and a taxane and no more than 2 prior regimens in metastatic setting. Eribulin was administered as 1.4 mg/m² i.v. over 1–2 min on day 1 and 8 of a 21 day schedule. Patients were classified in two strata based on taxane-sensitivity. Data of 41 enrolled patients is available. In the taxane sensitive stratum (progression >90 days after taxane), 20 patients were enrolled; ORR was 15% (3 patients). Median number of cycles was 4 (range 1–14), SD was seen in 60% patients and median PFS was 6.3 months. In the taxane resistant stratum (progression during or <90 days after taxane) 21 patients were enrolled, but no response was seen. Median number of cycles was 2 (range 1–7), SD was seen in 24% patients and median PFS was 1.2 months. Grade 3 or 4 drug related toxicities seen were predominantly hematological (46% patients; including one episode of febrile neutropenia) and less commonly non-hematological (20% patients; including one grade 3 neuropathy in course 9). Thus eribulin showed encouraging activity in taxane sensitivity cohort which was expanded to accrue up to another 25 patients. Results of this are awaited [60].

6.2.3. Prostate cancer—In the first multicenter, open-label, single-arm, phase II study in metastatic castration resistant prostate cancer (CRPC) patients, eribulin was administered as 1.4 mg/m² i.v. bolus (2–5 min infusion) on days 1 and 8 of a 21-day cycle. Patients were eligible if they had bilateral orchiectomy or other primary hormonal therapy with evidence of treatment failure. Primary efficacy endpoint was prostate-specific antigen (PSA) response rate, based on Bubley criteria, defined as two consecutive 50% decreases in PSA levels from baseline. Secondary endpoints were duration of PSA response and ORR by RECIST. In total 108 patients with median age of 71 years were evaluable for safety. Median number of treatment cycles was 4 (range 1–25). Patients were stratified by prior taxane exposure. In the taxane pretreated strata 50 patients received eribulin (safety population) of which 47 were evaluable as per protocol (eligible population). Median PSA at baseline was 123.0 ng/mL (range 6.0–9568.0). Among the eligible population 8.7% patients had 50% decrease in PSA, the ORR was 0% and median duration of PSA response could not be calculated. The 6 month PFS and 12 month OS were 12.6% and 57.2% respectively. Treatment related grade 3 and 4 toxicities in safety population were neutropenia (40%), leukopenia (16%), fatigue (8%, no grade 4) and peripheral neuropathy (6%, no grade 4). In the taxane naïve strata 58 patients were treated, all evaluable as per protocol (safety population = eligible population). Median PSA at baseline was 50.2 ng/mL (range 7.6–1154.0). 22.8% patients had 50% decrease in PSA. The ORR was 8.8% and median duration of PSA response was 96 days. The 6 month PFS and 12 month OS were 19.6% and 73.5% respectively. Treatment related grade 3 and 4 toxicities in safety population were neutropenia (22.4%), leukopenia (8.6%) and fatigue (6.9%, no grade 4). The results demonstrated some eribulin activity in metastatic CRPC patients with taxane naïve disease [61].

In a second multicenter ECOG trial, 119 progressive metastatic CRPC patients were treated with eribulin following same dose and schedule as earlier trial. In total 116 patients were eligible for the primary response determination. Median age of patients was 70 years and median number of treatment cycles was 4 (range 1–20+). This non-comparative study stratified patients to either a chemonaïve, prior-taxane only, or two prior cytotoxic chemotherapy arms. The trial was powered to detect a 50% PSA reduction using Consensus Criteria [62] in at least 40% versus 20% (90% power, one-sided $\alpha = 0.10$) for the chemonaïve stratum and 25% versus 10% (power 87%, one-sided $\alpha = 0.10$) for the taxane and two prior cytotoxic chemotherapy strata. In the chemonaïve arm (41 patients) 24% had 50% PSA response, 15% had SD for more than 9 weeks and 8% (of 26 patients with measurable disease) showed response. Median duration of PSA response was 7.1 months and median OS (in months) was not reached. In prior taxane arm (51 patients) 10% had 50% PSA response, 20% had SD for more than 9 weeks and 3% (of 38 patients with measurable disease) showed response. Median duration of PSA response was 3.6 months and median OS was 11.4 months. In the “two prior cytotoxic chemotherapy regimens” arm (51 patients) 4% had 50% PSA response, 29% had SD for more than 9 weeks and 8% (of 13 patients with measurable disease) showed response. Median duration of PSA response cannot be evaluated and median OS was 13.7 months. Among eligible patients who received treatment, 65 had dose modifications (both planned and unplanned). Treatment related grade 3/4 adverse events (frequency 10%) in taxane naïve, prior taxane and two prior chemotherapies respectively were neutropenia (52%, 50%, 68%), leukopenia (33%, 44%, 52%), fatigue (17%, 8%, 12%) and sensory neuropathy (14%, 16%, 4%). In the chemonaïve strata PSA response rate was 24%, much below the anticipated 40% rate. Thus although eribulin demonstrated some activity in metastatic CRPC with taxane-naïve disease, the overall response rate was not sufficient to warrant further studies in CRPC [63].

6.2.4. Ovarian cancer—Based on activity of eribulin in NIH:OVCAR-3 human epithelial ovarian cancer (EOC) xenograft model a multi-centric phase II study in recurrent epithelial ovarian, fallopian tube or peritoneal cancer was conducted. Eribulin was administered as 1.4 mg/m² infusion over 15 min on 1 and 8 days of every 21 days cycle. The eligibility criteria for patients included EOC, fallopian tube or peritoneal cancer with measurable disease, progression-free interval of <6 months since last platinum-based therapy and 2 prior cytotoxic regimens. Patients were stratified based on prior platinum sensitivity. The primary objective was to determine the ORR and secondary objective was to assess the toxicity profile [64]. In the platinum resistant epithelial ovarian cancer (PREOC) stratum 36 patients with median age of 61 years were enrolled of which 35 were evaluable for response. The median platinum-free interval was 3 months (range 0.1–5.9 months). All patients received platinum-taxane as first-line treatment. Observed ORR was 5.7% (all PRs = 2, with DOR of 84 days and 128 days). Time to objective response (PR) was 2.8 months in both. SD was seen in 16/35 (46%) patients. Median PFS was 2 months (range 1–7 months). Eribulin related grade 3–4 toxicities (< 10% in safety population) were: neutropenia 44% and leukopenia 31%. Thus eribulin had minimal activity in PR-EOC with ORR of only 5.7%. Activity of eribulin in platinum-sensitive patients is being studied in a separate stratum [65].

6.2.5. Sarcoma—EORTC 62052 assessed the efficacy and safety of eribulin mesylate in 4 independent strata of patients with soft tissue sarcoma namely leiomyosarcoma, adipocytic, synovial and other subtypes of soft tissue sarcomas (Table 4). Patients with intermediate or high grade soft tissue sarcomas with 2 previous chemotherapies (up to 2 single agents or 1 combination) for advanced disease and documented progression were eligible. Eribulin, 1.4 mg/m² (i.v.) was given over 2–5 min on days 1 and 8 every 3 weeks until intolerance or progression. The primary end point was the progression-free rate at 12 weeks (PFR_{12weeks}) using RECIST. Secondary end points included OS, PFS, ORR, CBR, time to onset of

response, DOR and safety assessments. A Simon 2-stage design was applied (P1: 40%; P0: 20%; $\alpha = \beta = 0.1$) per stratum. Histopathology and responses were reviewed. Important grade 3–4 common treatment-related toxicities included leukopenia, neutropenia, anemia, fatigue, febrile neutropenia, increased ALT and infection without neutropenia in 33%, 50%, 9%, 4%, 3%, 3% and 3% of patients respectively. A tabulated result of different strata is presented in Table 5. The results showed that eribulin has a tolerable profile in pretreated patients with soft tissue sarcomas and showed responses ranging from CR, PR to SD in various subgroups. Further studies are warranted in leiomyosarcoma and adipocytic sarcoma subgroups, as the PFR_{12weeks} reached predefined statistical targets [66].

6.2.6. Pancreatic cancer—Based on preclinical studies suggesting eribulin's efficacy in pancreatic cancer models, an open label multi-centric phase II study in pancreatic cancer as second line therapy was conducted. Eligibility criteria included histologically confirmed; locally advanced, unresectable or metastatic pancreatic adenocarcinoma with measurable disease and evidence of disease progression after gemcitabine therapy. The primary objective of this study was to determine ORR (CR + PR). Patients received eribulin mesylate 1.4 mg/m² i.v. on days 1 and 8 every 3 weeks. In total 14 patients (of 15 accrued) received treatment and 12 were evaluable for response. The median age of accrued patients was 61 years and they received a median number of two cycles (range 1–15). Response was assessed by CT scans every 6 weeks. No CR or PR was observed but SD as best response was seen in 42% (5/12) patients. Of these 5 patients, 3 had SD for 12 cycles (more than 9 months) or greater. Thus eribulin was well tolerated but it did not result in any objective responses in refractory pancreatic cancer. However, 42% of patients had SD and for 3 patients this was maintained for more than 9 months. Grade 3 and 4 toxicities encountered were neutropenia, fatigue, peripheral neuropathy and thrombosis in frequency of 29%, 14%, 7% and 7% respectively. Thus seeing a tolerable profile and long term disease control further studies in pancreatic cancer may be warranted [67].

6.2.7. Urothelial tract cancer (UC) and renal insufficiency (UCD)—Antitubulin agents have activity in UC. Also eribulin has minimal renal excretion with <10% excreted unchanged in urine. Thus eribulin can be of potential benefit in locally advanced and metastatic UC patients, particularly with renal dysfunction. After encouraging activity of eribulin in UC in phase I renal dysfunction study [53], subsequent phase II part of this multi-centric trial is currently being conducted. Initially, only patients without renal insufficiency were to be enrolled until the phase II dose (MTD) was proved safe. Accrual of patients with renal insufficiency would then begin at this dose [68]. In the first part of phase II trial, patients with normal creatinine or calculated creatinine clearance ≥ 60 mL/min and any histologically or cytologically confirmed urothelial cancer without prior cytotoxic therapy for advanced disease (though allowed neo and adjuvant therapies) were accrued. Eribulin 1.4 mg/m² was given IV on day 1 and 8 every 21 days. The primary objective was response rate evaluation as defined by RECIST in a 2-stage design (requiring 2 responses in 21 patients to proceed to a total of 41 pts). The secondary objectives are PFS, OS and toxicity assessment. In total 40 patients with median age of 67 years entered the trial. Accrued patients included transitional (35), adenocarcinoma (3), squamous (1) and small cell (1) with 72.5% patients having prior neo/adjuvant chemotherapy. Patient percentage in Bajorin risk groups 0, 1 and 2 were 30%, 57% and 13% respectively. Based on 37 evaluable patients, ORR was found to be 38% (1 CR and 14 PR). Of the 15 responses 13 were in transitional cell cancer patients (37% response rate). In patients with prior neo/adjuvant chemotherapies the response rate was 34%. At median follow-up of 19.8 months, median PFS was 3.9 months, median OS was 9.4 months. A significant correlation was found between PFS and Bajorin risk group ($p = 0.028$ for trend). Important drug related grade 3 and 4 toxicities included neutropenia, hyponatremia, hyperglycemia, leg fatigue with aching and sensory

neuropathy in 20, 4, 3, 1 and 1 patients, respectively. The results showed eribulin as a single agent has significant activity in UC to warrant further investigations. Currently accrual is ongoing for patients with creatinine clearance <40 mL/min in whom the 1.4 mg/m² dose studied is also tolerable [69].

6.2.8. Squamous cell carcinoma of the head and neck—A multi-centric phase II trial to evaluate eribulin response in patients with metastatic or recurrent squamous cell carcinoma of the head and neck (SCCHN) was conducted with NCI collaboration [70]. The primary objective was assessment of response (confirmed CR and PR). Secondary objectives were PFS, OS and toxicity assessment. Eligibility criteria included patients with no prior chemotherapy for metastatic or recurrent SCCHN. Induction or adjuvant therapy was limited to one. A total of 40 eligible patients with median age of 61.2 years and Zubrod Performance Status of 0 (48%) and 1 (53%) were enrolled. Thirty-three patients (83%) had metastatic disease. Primary tumor sites included oropharynx, lip/oral cavity, larynx, hypopharynx, other/unknown and nasopharynx in 15, 12, 6, 4, 2 and 1 patient respectively. Patients received eribulin mesylate at 1.4 mg/m² on Days 1 and 8 of an every 21-day cycle. Common Grade 3 and 4 toxicities included lymphopenia, leukocytopenia, neutropenia, hyponatremia, fatigue, diarrhea and dyspnea in 15%, 13%, 10%, 5%, 5%, 5% and 5% of population respectively. One treatment-related death due to pulmonary hemorrhage occurred at treatment initiation. Among 40 assessable patients, two confirmed and one unconfirmed PRs were observed and 19 patients had SD. An estimated confirmed response rate of 5% (95% confidence interval: 1–17%) was observed. The estimated median PFS was 3 months (95% confidence interval: 1–3 months) and estimated median OS was 7 months (95% confidence interval: 5–10 months). Thus although eribulin was well tolerated in metastatic or recurrent SCCHN, it did not show any significant efficacy in terms of median PFS [70].

6.3. Phase III studies

The encouraging results of eribulin in MBC patients led to its investigation in two randomized, controlled phase III studies in patients with locally advanced/recurrent or MBC previously treated with an anthracycline and a taxane [71].

The first of these trials was named “EMBRACE” (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389; NCT00388726; Study 305), an open-label, multicenter (137), randomized, controlled, parallel-group phase III study in heavily pretreated MBC patients to compare OS with eribulin to real-life choices. Inclusion criteria included women (>18 years) with locally recurrent or MBC previously treated with 2–5 prior chemotherapies (>2 for advanced disease), including an anthracycline and a taxane. Patients were randomized in 2:1 to eribulin (1.4 mg/m² 2–5 min IV bolus on days 1 and 8 of a 21-day cycle) or treatment of physician's choice (TPC). TPC included any approved monotherapy (cytotoxic, hormonal, biologic), radiotherapy or supportive care only administered according to local practice and defined before randomization. The primary endpoint was to compare OS as with eribulin monotherapy to TPC in the described patient population. Secondary endpoints were ORR and PFS by independent review, and DOR. Safety and tolerability were also assessed. Tumor assessments were performed every 8 weeks (±1 week), or sooner if there was a suspicion of disease progression. In all, 762 (508 eribulin, 254 TPC) patients with median age of 55.2 years were treated. Of these 16% were HER2-positive and 19% were triple-negative. Median number of prior chemotherapy regimens was 4 and 73% of them had received prior capecitabine.

Median OS was 13.1 months for eribulin and 10.6 months for TPC, $p = 0.04$ (primary analysis, stratified log rank test; HR 0.81; 95% CI 0.66, 0.99). Median PFS was 3.7 months for eribulin and 2.3 months for TPC, $p = 0.09$ (HR 0.85; 95% CI 0.70, 1.03). ORR was 12%

(0.4% CR, 11.5% PR) for eribulin and 5% (0 CR; 5% PR) for TPC, $p = 0.005$. Grade 3/4 treatment-related adverse events of interest for eribulin were neutropenia, asthenia/fatigue and peripheral neuropathy in 44%, 7.6%, and 8.4% respectively. Ten percent of the patients experienced treatment-related serious adverse events which was more in the eribulin arm (12%) as compared to TPC arm (7%). The study met its primary endpoint with a significant improvement in OS by a median of 2.5 months in favor of eribulin. Eribulin demonstrated a manageable tolerability profile, acceptable for a chemotherapy agent to be used as monotherapy in this late-line setting. Results from EMBRACE also showed that a secondary endpoint of ORR was statistically significant. But another secondary endpoint, PFS, though supportive of the primary endpoint did not reach statistical significance and was out of proportion with the improvement in observed OS. However, since this was a study with OS as primary endpoint, many patients entered the study without measurable disease and were therefore censored in the independent review. Investigator reported PFS was statistically significant, as was PFS by independent review and investigator review for the Per Protocol population. The response rate to eribulin, although significant (12.2% with eribulin versus 4.7% with TPC; $P = .002$), was on the lower side. Eribulin was associated with more but acceptable febrile neutropenia (grade 3/4 in 4.6% of patients versus 1.6% for TPC) and neuropathy (grade 3/4 in 8.4% of patients versus 2% for TPC) [20,71,72]. The pre-defined subgroup analyses showed that as compared to TPC, eribulin maintained an OS benefit irrespective of hormone receptor status, extent of disease and prior therapy [73]. Table 5 presents comparative data of eribulin in EMBRACE study with other neuropathy inducing chemotherapeutic agents used in breast cancer.

Another open-label, multicenter, randomized, controlled, parallel-group phase III study is ongoing where eribulin is being assessed as a second-line therapy for metastatic disease. The primary objective is to compare eribulin and capecitabine in terms of OS and PFS. Secondary objectives include assessments of response data, DOR, 1-, 2- and 3-year survival, quality of life (QOL; using the European Organization of Research and Treatment of Cancer, EORTC questionnaire), pain intensity [via a Visual Analogue Scale (VAS) and analgesic consumption], safety and assessment of pharmacokinetic/pharmacodynamic relationships for eribulin. Eligibility criteria included women (≥ 18 years) with histologically or cytologically confirmed locally advanced or MBC with ≤ 3 previous chemotherapeutic regimens (but ≤ 2 regimens for locally advanced or MBC) including an anthracycline and a taxanes with documented progression. In this study, 1102 enrolled patients are randomized (1:1) to receive either eribulin or capecitabine (with approximately 550 patients in each arm). The eribulin dose is the same as EMBRACE trial (1.4 mg/m^2 ; 2–5 min IV bolus on days 1 and 8 of a 21-day cycle). In the capecitabine arm, patients receive capecitabine $2.5 \text{ g/m}^2/\text{day}$ administered orally twice daily in two equal doses on days 1–14 every 21-days cycle. Tumor assessments are carried out every 2 cycles (each of 3 weeks' duration) and every third cycle subsequently starting with cycle 15. Enrollment has been completed and estimated study completion and reporting date is January 2012 [71].

7. Conclusions

Eribulin mesylate is a novel drug which has shown a significant activity and efficacy in heavily pretreated refractory breast cancer patients in phase III trials and has also progressed in phase II trials in several cancer subtypes. The main treatment related toxicities are fatigue and neutropenia which are manageable and the incidence of peripheral sensory neuropathy is comparatively low. Though it is hard to compare different single agents in MBC on the basis of phase III studies due to wide contrast in the protocol population in such studies (Table 5), EMBRACE accrued a population cohort which was more heavily pretreated than seen in earlier studies and is representative of what is seen in daily clinical practice. Eribulin showed a lower incidence of severe neuropathy as compared to ixabepilone and paclitaxel.

Also the incidence of grade 3/4 neutropenia with eribulin was comparatively less than with ixabepilone, vinorelbine and docetaxel as observed from phase III trials cumulative data. Eribulin showed a statistically significant OS which was not seen with a recently approved drug, ixabepilone. However PFS statistical significance seen with ixabepilone is not seen with eribulin (Table 5). The low probability of drug–drug interactions in clinical setting, easy administration as bolus, low hypersensitivity chances and full tolerability in renal dysfunction patients are of additional benefit. The EMBRACE study has for the first time in the history of breast cancer clinical trials demonstrated a survival benefit of monotherapy in the third line (or beyond) setting, compared to a variety of agents used in the real-world setting. Preclinical studies to produce second generation structurally modified analogues with increased oral bioavailability, brain penetration and efficacy against multidrug resistant tumors as well as attenuated Pgp mediated drug efflux are currently ongoing [74].

The spectrum of action of eribulin is similar to that of vinca alkaloids. Eribulin has shown an appreciable ORR of 9.3–21.3% in breast and 9.7–15% in NSCLC. Vinorelbine is an acceptable chemotherapeutic agent that can be used in the treatment of these two cancers [87]. However eribulin has shown a low ORR of 0%, 5%, 3–8.8% and 5.7% in pancreatic, head and neck, prostate and ovarian cancers respectively. Similarly, vinorelbine is not recommended as a chemotherapeutic option in any of these malignancies. Also, the ORR of eribulin clearly falls within the 95% CI of the RR with vinorelbine, the most commonly used vinca alkaloid [87].

On November 15, 2010, eribulin was approved as a third line therapy for patients with MBC, previously treated with an anthracycline and a taxane by the U.S. Food and Drug Administration (U.S.FDA). The recommended dose of eribulin in normal, mild hepatic (Child Pugh A), moderate hepatic (Child Pugh B) and moderate renal impairment (creatinine clearance 30–50 mL/min) is 1.4, 1.1, 0.7 and 1.1 mg/m² respectively, as a 2–5 IV min bolus on days 1 and 8 of 21-day cycle [19]. Based on all the available data eribulin is a suitable choice for third line monotherapy in MBC patients. Further studies in lung, pancreas, sarcoma subtypes and bladder cancers are warranted along with combination trials in breast and lung cancer.

Biography

Sanjay Goel, M.D., M.S. is a faculty member in the Department of Oncology at Montefiore Medical Center, and an Associate Professor of Medicine at the Albert Einstein College of Medicine in Bronx, New York. He completed his residency training in internal medicine in 1999 and subsequently finished his fellowship training in hematology and medical oncology in 2002, in which he is certified by the American Board of Internal Medicine. He also completed a 2-year degree course obtaining an MS degree in clinical research from the Albert Einstein College of Medicine in 2003. He has an interest drug development of anti-cancer agents and has extensive experience in carrying out early phase clinical trials in collaboration with industry and the NCI and with investigator initiated trials. He is currently engaged in numerous clinical trials, in phase I, and in phase II and III trials in gastrointestinal and genitourinary malignancies. He has presented his findings at national and international meetings and has published in a wide variety of journals.

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Fig. 1.
Chemical structure of halichondrin B.

Fig. 2.
Chemical structure of eribulin mesylate.

Fig. 3.
Mechanism of action of eribulin (courtesy Eisai).

Fig. 4. Plasma C_{max} versus dose following a 1-h infusion of eribulin on day 1. (B) Plasma area under the concentration–time curve (AUC_{0-8}) versus dose following a 1-h infusion of eribulin on day 1. (C) Plasma concentration versus time profile for the 1.0 mg/m^2 treatment group ($n = 9$).
From: Ref. [10].

Fig. 5. Eribulin related adverse events of interest or 10% incidence as seen in 394 patients with MBC [55,56].

Table 1

Eribulin pharmacokinetics comparison in normal, mild and moderate hepatic impairment.

	Normal hepatic function	Mild hepatic impairment (Child-Pugh A)	Moderate hepatic impairment (Child-Pugh B)
Dose on day 1 (mg/m ²)	1.4	1.1	0.7
Clearance (L/h)	4.57	2.75	1.96
Elimination half life (h)	36.1	41.1	65.4
Mean dose normalized C _{max} (ng/mL/mg)	72	84	111
Mean dose normalized AUC _(0-∞) (ng h/mL/mg)	229	420	720

Table 2

Summary of phase I trials.

Trial	Total patients	Schedule	Maximum tolerated dose (mg/m²)	Dose limiting toxicity (DLT)
Synoldetal. [41]	40	Weekly bolus 3 weeks out 4	1.4	Febrile neutropenia and neutropenia
Goel et al. [10]	32	1-h weekly infusion 3 weeks out of 4	1.0	Neutropenia
Tanetal. [43]	21	1-h infusion on day 1 of 21-day cycle	2.0	Febrile neutropenia
Minami et al. [44]	15	Weekly bolus 2 weeks out of 3	1.4	Febrile neutropenia and neutropenia
Synold et al. [53]	21	Weekly on day 1 and 8 every 21 days in renal dysfunction	Moderate-1.4 Severe-1.4	Moderate-No Severe-Grade 3 weakness + fatigue
Goel et al. [54] ^a	21	E/G given weekly 3 weeks out of 4. Due to DLT, regimen changed in CT 2 with E/G given weekly 2 weeks out of 3	E 1.0 and G 1000 every 3 weeks	Grade 3 diarrhea and grade 3 fatigue
Swami et al. [47] ^a	52	C given as 30-min IV infusion (Day 1) and E by 2- to 5-min IV bolus (Day 1 and 8), separated by 1 h every 21 days	E 1.1 mg/m ² , C AUC 6	Neutropenia and febrile neutropenia

^aOngoing E, Eribulin; G, Gemcitabine; C, Carboplatin; CT, Cohort.

Phase II trials in metastatic breast cancer patients.

Table 3

Trial	Protocol population	ORR, CR, PR (%)	CBR (%)	Median DOR (days)	Median PFS (days)	Median OS (days)	6-month PFS (%)	6-month OS (%)	Most common grade 3/4 toxicities (%)	Grade 3 neuropathy (%) ^a	Grade 3-4 neutropenia (%)	Febrile neutropenia (%)
Vahdat et al. [56]	87	11.5,0, 11.5	17.2	171	79	275	25.9	67.8	Neutropenia, leukopenia, fatigue	5	64	4
Cortes et al. [55]	269	9.3, 0, 9.3	17.1	106	78	315	12.4	72.3	Neutropenia, leukopenia, fatigue	6.9	54	5.5
Iwata et al. [57]	81	21.3,0,21.3	27.5	119	112	331	20.1	72.3	Neutropenia, leukopenia, febrile neutropenia	3.7	95.1	13.6

CBR, Clinical benefit rate (defined as CR + PR + SD > 6 months).
PFS, progression free survival; OS, overall survival; PR, partial response.
DOR, duration of response; CR, complete response.
ORR, overall objective response rate = [(CR + PR)/number of eligible patients].

^aNo grade 4 peripheral neuropathy in any trial.

Table 4

Comparison of eribulin efficacy in sarcoma subtypes.

Sarcoma type	Number of patients	Evaluable patients	PFR _{12weeks} (%)	Median PFS (months)	Median OS (months)	OS after 1 year (%)
Leiomyo	39	12	32	3	20	70
Adipocytic	38	33	45	3	10	48
Synovial	19	19	21	3	11	36
Other	32	26	19	2	6	30

OS, overall survival; PFS, progression free survival; PFR_{12weeks}, progression free rate at 12 weeks.

Comparative data of EMBRACE study with other neuropathy inducing chemotherapeutic agents used in breast cancer.

Table 5

Study	Patient profile	Therapy	Treated number of patients	Median OS	Median PFS/TTP	ORR, CR, PR	Median DOR (m)	Important G 3-4 toxicities	G 3-4 peripheral neuropathy (%)	G 3-4 neutropenia (%)	G 3-4 febrile neutropenia	G 3-4 fatigue (%)
Twelves et al. (2010) [19,72]	2-5 prior CT including an anthracycline and a taxane	Comparator Eribulin 1.4 mg/m ² 2-5 min IV bolus on days 1 and Sofia 21-day cycle	508	13.1 months	PFS 3.7 months	12, 0.4, 11.5	4.1	Fatigue, neutropenia, peripheral neuropathy	8.4	44	4.6	7.6
Thomas et al. (2007) [75,76]	3 prior CT regimens, anthracycline-pretreated or -resistant and taxane-resistant	Treatment of physician's choice – any monotherapy (cytotoxic, hormonal, biologic) or supportive care only	254	10.6 months (<i>p</i> = 0.04)	PFS 2.3 months (<i>p</i> = 0.09)	5, 0, 5	6.7	Neutropenia, fatigue, anemia	2	23	1.6	11
		Isxabipilone (40 mg/m ² IV on day 1) plus capecitabine (2000 mg/m ² PO on days 1-14) of a 21-day cycle	369	12.9 months	PFS 5.8 months	34.7, <1, 34	6.4	Neutropenia, Peripheral neuropathy, hand-foot syndrome	22.8	68	4.8	9
		Capecitabine alone 2500 mg/m ² PO on the same schedule	368	11.1 months (<i>p</i> = 0.19)	PFS 4.2 months (<i>p</i> =0.0003)	14.3, 0, 14	5.6	Hand-foot syndrome, neutropenia, diarrhea	0	11	0.5	3.3
Sparano et al. (2010) [77]	2 prior CT regimens including an anthracycline and a taxane	Isxabipilone (40 mg/m ² IV on day 1) plus capecitabine (2000 mg/m ² PO, day 1-14) of a 21 day cycle	595	16.4 months	PFS 6.24 months	43.3, 3, 40	6.1	Neutropenia, Peripheral neuropathy, hand-foot syndrome	24.7	72	7	11.8
Martín et al. (2007) [78]	2 prior CT regimens including an anthracycline and a taxane	Capecitabine alone 2500 mg/m ² PO on the same schedule	603	15.6 months (<i>p</i> = 0.1162)	PFS 4.4 months (<i>p</i> =0.0005)	28.8, 2, 26	6.3	Hand-foot syndrome, diarrhea, neutropenia	1.2	9	0.6	3.2
		Gencitabine plus vinorelbine (1200/30mg/m ² , IV days 1 and 8) every 21 days	123	15.9 months	PFS 6.0 months	36.5, 31	4.8	Neutropenia, fatigue, febrile neutropenia	2.4	61	11	24
		Vinorelbine (30mg/m ² , IV days 1 and 8) every 21 days	125	16.4 months (<i>p</i> = 0.80)	PFS 4.0 months (<i>p</i> = 0.0028)	26.5, 21	3.7	Neutropenia, fatigue, febrile neutropenia	4	44	6	17
Jones et al. (1995) [79]	2CT regimens, anthracycline pretreated	Vinorelbine 30 mg/m ² IV weekly	115	35 weeks	TTP 12 weeks	16, 5, 11	UNK	Neutropenia, anemia, fatigue	2	75	UNK	4
		Melphalan 25 mg/m ² IV every 4 weeks	64	31 weeks (<i>p</i> = 0.34)	TTP 8 weeks (<i>p</i> <0.001)	9, 2, 7	UNK	Neutropenia, thrombocytopenia, anemia	0	69	UNK	3

Study	Patient profile	Therapy	Treated number of patients	Median OS	Median PFS/TTP	ORR, CR, PR	Median DOR (m)	Important G 3–4 toxicities	G 3–4 peripheral neuropathy (%)	G 3–4 neutropenia (%)	G 3–4 febrile neutropenia	G 3–4 fatigue (%)
Harvey et al. (2006) [80]	Failure of a single prior CT regimen or relapse within 6 months of adjuvant CT	Docetaxel 60 mg/m ² IV every 3 weeks	151	10.6 months	TTP 13.7 months	22.1, 2.5, 19.7	34.4–36.7	Neutropenia, leukopenia, febrile neutropenia	1.3	76.4	4.7	2.7
		Docetaxel 75 mg/m ² IV every 3 weeks	188	10.3 months	TTP 13.9 months	23.3, 1.4, 21.9	34.4–36.7	Neutropenia, leukopenia, febrile neutropenia	1.6	83.7	7.4	8.4
		Docetaxel 100 mg/m ² IV every 3 weeks	188	12.3 months	TTP 18.6 months	36, 6.5, 29.5	34.4–36.7	Neutropenia, leukopenia, febrile neutropenia	4.9	93.4	14.1	14.6
Miles et al. (2010) [81]	HER2-negative, locally recurrent or MBC	Placebo + docetaxel 100 mg/m ² q3w	238	31.9 months	PFS 8.1 months	46.4, UNK, UNK	6.6	Neutropenia, febrile neutropenia, asthenia	2.2	17.3	11.3	5.2
		Bevacizumab 7.5 mg/kg + docetaxel 100 mg/m ² q3w	247	30.8 months (<i>p</i> = 0.72)	PFS 9 months (<i>p</i> = 0.045)	55.2, UNK, UNK	8.1	Neutropenia, febrile neutropenia, fatigue	3.2	19.8	15.1	9.5
		Bevacizumab 15 mg/kg + docetaxel 100 mg/m ² q3w	245	30.2 months (<i>p</i> = 0.85)	PFS 10 months (<i>p</i> < 0.001)	64.1, UNK, UNK	8.3	Neutropenia, febrile neutropenia, asthenia	4.5	19.8	16.2	6.5
Joensuu et al. (2010) [82]	No previous CT for advanced breast cancer	Docetaxel 100 mg/m ² q3w (later amended to 80 mg/m ²)	115	28 months	TTP 11.7 months	84, 71, 13	10.9	Neutropenia, absent or irregular menstrual cycle, febrile neutropenia	UNK	99.1	27.4	23.9
		Docetaxel 100 mg/m ² q3w (later amended to 80 mg/m ²) + gemcitabine 1000 mg/m ² days 1 and 8 every 3 weeks	122	27 months (<i>p</i> = 0.60)	TTP 11.3 months (<i>p</i> = 0.72)	75, 65, 22	12.9	Neutropenia, absent or irregular menstrual cycle, febrile neutropenia	UNK	95.9	32	20.5
Miller et al. (2007) [83]	No previous CT for MBC	Paclitaxel 90 mg/m ² day 1, 8, 15 every 4 weeks + bevacizumab 10 mg/kg day 1, 15 every 4 weeks	365	26.7 months	PFS 11.8 months	49.2, UNK, UNK	UNK	Sensory neuropathy, hypertension, infection	23.5	0	0.8	9.1
		Paclitaxel 90 mg/m ² day 1, 8, 15 every 4 weeks	346	25.2 months (<i>p</i> = 0.16)	PFS 5.9 months (<i>p</i> < 0.0001)	25.2, UNK, UNK, UNK	UNK	Sensory neuropathy, fatigue, infection	17.7	0.3	0	4.9
Seidman et al. (2008) [84]	1 CT regimens for MBC	Paclitaxel 175 mg/m ² every 3 weeks (later amended to add trastuzumab to HER–2+; HER–2 non-overexpressors randomly assigned to trastuzumab)	227 (+158 from CALGB 9342 protocol)	1.36 years	TTP 0.43 years	29, UNK, UNK	UNK	Neuropathy, neutropenia, lymphopenia	12	15	4	5
		Paclitaxel 80 mg/m ² weekly (later amended to	350	2.02 years (<i>p</i> = 0.0092)	TTP 0.72 years (<i>p</i> < 0.001)	42, UNK, UNK	UNK	Neuropathy, neutropenia, lymphopenia	24	9	3	6

Study	Patient profile	Therapy	Treated number of patients	Median OS	Median PFS/TTP	ORR, CR, PR	Median DOR (m)	Important G 3–4 toxicities	G 3–4 peripheral neuropathy (%)	G 3–4 neutropenia (%)	G 3–4 febrile neutropenia	G 3–4 fatigue (%)
add trastuzumab to HER –2+; HER–2 non-overexpressors randomly assigned to trastuzumab)												
Bishop et al. (1999) [85]	No previous CT for advanced disease	Paclitaxel 200 mg/m ² IV every 21 days for eight cycles (24 weeks)	107	17.3 months	PFS 5.3 months	29, 2, 27	UNK	Neutropenia, arthralgia, neuropathy	10	67	10	UNK
		Cyclophosphamide 100 mg/m ² /day (PO; days 1–14), methotrexate 40 mg/m ² (IV; days 1 and 8), fluorouracil 600 mg/m ² (IV; days 1 and 8), and prednisone 40 mg/m ² /day (PO; days 1–14) repeated every 28 days for six courses (24 weeks)	102	13.9 months (<i>p</i> =0.068)	PFS 6.4 months (<i>p</i> =0.25)	35, 6, 29	UNK	Neutropenia, thrombocytopenia, fever	0	73	27	UNK
Gradishar et al. (2005) [86]	Not received paclitaxel or docetaxel for MBC	Albumin-bound paclitaxel 260 mg/m ² IV every 3 weeks	229	65 weeks	TTP 23 weeks	33, UNK, UNK	UNK	Neuropathy, fatigue, neutropenia	10	≈30	<2	≈5
		Paclitaxel 175 mg/m ² IV every 3 weeks	225	55.7 weeks (<i>p</i> =0.374)	TTP 16.9 weeks (<i>p</i> = 0.006)	19, UNK, UNK	UNK	Neuropathy, neutropenia, fatigue	2	≈45	<2	≈1

ORR, objective response rate; PFS, progression free survival; OS, overall survival.

DOR, duration of response; CR, complete response; PR, partial response.

TPC, treatment of physician's choice; G, grade TTP-Time to progression.

UNK, unknown.